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(54) Title: USE OF CERTAIN XANTHINE DERIVATIVES AND THEIR PHARMACEUTICALLY ACCEPTABLE SALTS FOR THE MANUFACTURE OF A MEDICAMENT USEFUL FOR COUNTERACTING HYPOCLYCAEMIA

(57) Abstract

Use of certain xanthine derivatives and their pharmaceutically acceptable salts for the manufacture of a medicament useful for counteracting hypoclycaemia.

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Use of certain xanthine derivatives and their pharmaceutically acceptable salts for the manufacture of a medicament useful for counteracting hypoclycaemia.

Field of the invention

The present invention relates to the use of a xanthine derivative of formula (I) in the manufacture of a pharmaceutical composition for counteracting hypoglycaemia in diabetic patients and to the use of a pharmaceutical composition comprising a compound of formula (I) for counteracting hypoglycaemia in diabetic patients.

Background of the invention

The normal glucose level in human whole blood is in the range 3.9 - 5.6 mmol/l. The blood glucose level rises in connection with meals and then gradually declines to approach the fasting level during the next few hours. The minimum value attained before the next rise is usually designated the nadir level. In insulin dependent diabetic patients an overdosing of insulin or a too modest food consumption may lead to hypoglycaemia, i.e. blood glucose levels lower than the normal values. If the blood glucose level declines to about 2.5 mmol/l - with individual variations - hypoglycaemia manifests itself by very unpleasant symptoms such as confusion, weakness, dizziness, headache, sweating, visual disturbance and hunger. Ultimately, if untreated, hypoglycaemia may lead to convulsions, unconsciousness, coma and even to death.

Usually hypoglycaemia can be relieved by administration of glucose or glucagon. Normally, but not always, a hypoglycaemic episode is preceded by some early warning symptoms which makes it possible for the patient to take measures against it. Throughout this specification the diabetic patients' attention to these early warning symptoms is in accordance with the common usage referred to as the "awareness".

According to a widely acknowledged, modern regimen for treating insulin dependent diabetic patients, the dosing of the insulin is adjusted so as to keep the blood glucose level as close to the normal values as possible. This is achieved by administering the daily amount of insulin as one large dose of a more or less protracted preparation to cover the basal demand, supplemented by a number of smaller doses of a rapid-acting preparation to be taken as needed e.g. in connection with meals.

According to the regimen earlier relied upon the daily amount of insulin was administered in the form of a few relatively large, fixed doses. For diabetic patients the modern regimen which tends to mimic the insulin level in non-diabetic persons in several ways improves the quality of life. Thus, it enables the patients to act more spontaneously as regards their intake of food and drink and as regards physical activity. Also the so-called long term complications seem to be less severe with a good metabolic control. Inherently, however, this modern regimen also implies that the gap between the actual blood glucose level and hypoglycaemia will in general be more narrow.

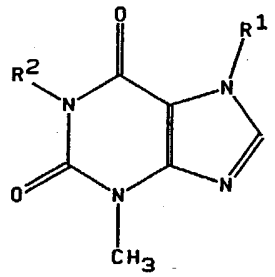
Diabetic patients are very anxious to avoid hypoglycaemic episodes, both because of the unpleasant immediate symptoms and because of the irreversible long term complications which may result from a less than optimal metabolic control. Therefore there is a strong need for the improvements provided by the present invention.

The use of medicaments based on xanthine derivatives is of long standing. Thus, caffeine has long been used as a CNS stimulant. Theobromine is a diuretic, a bronchodilator and a cardiotonic, and theophylline and many closely related compounds are smooth muscle relaxants. However, to the knowledge of the present inventor it has never been suggested to use xanthine derivatives for improving the awareness of diabetic patients who will then be in a better position to avoid

hypoglycaemia or for supporting the blood glucose recovery after hypoglycaemia.

Summary of the invention

In its broadest aspect the present invention relates to the use of a compound of the general formula (I):



(I)

wherein R^1 is hydrogen, methyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 2-nicotinoyloxyethyl, the nicotinic acid salt of 2-hydroxy-3-((2-hydroxyethyl)methylamino)propyl or a lone pair involved in salt formation with the 2-hydroxyethyltrimethylammonium ion and R^2 is hydrogen or methyl; a compound thereof with ethylenediamine or the pharmaceutically acceptable acid addition salts thereof in the manufacture of a pharmaceutical composition useful for counteracting hypoglycaemia in diabetic patients and to the use of a pharmaceutical composition comprising a compound of formula (I) for counteracting hypoglycaemia in diabetic patients.

According to a preferred embodiment of the present invention the compound of formula (I) is theophyllamine.

According to another preferred embodiment of the present invention the compound of formula (I) is theophylline.

According to a further preferred embodiment of the present invention the compound of formula (I) is choline theophyllinate.

According to a further preferred embodiment of the present invention the compound of formula (I) is proxyphylline.

According to a further preferred embodiment of the present invention the compound of formula (I) is glyphylline.

According to a further preferred embodiment of the present invention the compound of formula (I) is etofylline nicotinate.

According to a further preferred embodiment of the present invention the compound of formula (I) is xanthinol nicotinate.

According to a further preferred embodiment of the present invention the compound of formula (I) is caffeine.

According to a further preferred embodiment of the present invention the compound of formula (I) is theobromine.

Detailed description of the invention

The cause of clinical diabetes is always insulin deficiency. Insulin plays a major role in the regulation of carbohydrate, lipid and protein metabolism in insulin-sensitive cells and the most familiar of insulin's effects is its ability to promote glucose transport from the blood into the tissues whenever blood glucose levels exceed normoglycaemia. The major control of insulin secretion is exerted by a feedback effect of the blood glucose level directly on the pancreas. When the level of glucose in the blood perfusing the pancreas is elevated, insulin secretion in the pancreatic venous blood is increased; when the level is normal or low, the rate of insulin secretion is low. In healthy subjects the feedback control of blood glucose on insulin secretion operates with great precision, so that blood glucose and blood insulin levels parallel each other with remarkable consistency. On

the other hand patients suffering from type 1 diabetes have to take insulin and patients suffering from type 2 diabetes have to take either insulin or agents which stimulate the insulin producing β-cells of their pancreas in order i.a. to avoid hyperglycaemia. The insulin requirements depend on various factors: they rise in connection with meals, when patients gain weight, during pregnancy, during psychical stress and in the presence of infection and fever; they fall when patients lose weight and during exercise.

After careful instruction by medical staff most diabetic patients manage the day-to-day care of their disease themselves. Although the patients are usually very well trained in judging their own insulin requirements occational misjudgements some of which result in hypoglycaemia are inevitable.

Surprisingly it has now been found that compounds of formula (I) can be used for counteracting hypoglycaemia. In the present context the expression "counteracting hypoglycaemia" shall be construed to mean either "preventing the occurence of hypoglycaemic episodes" or "supporting the recovery after a hypoglycaemic episode".

As demonstrated in Table 1 and in Table 2 the nadir levels in healthy subjects as well as in diabetic patients are higher in the same person when theophyllamine is administered than with placebo. Thus, a hypoglycaemic episode is less likely to occur when theophyllamine is administered.

Similarly Table 1 and Table 2 demonstrate that blood glucose levels after 1 hour and after 2 hours are higher in the same person when theophyllamine is administered than with placebo. Thus the administration of theophyllamine supports the recovery after a hypoglycaemic episode.

Some diabetic patients who have taken theophyllamine regularly as a preventive measure have even experienced an improved awareness and may thus be able to take measures against a threatening hypoglycaemic episode at an earlier stage e.g. by the ingestion of glucose.

For counteracting hypoglycaemia in diabetic patients the preferred dose of the compound of formula (I) will generally be in the range from about 1 mg/kg body weight/day to about 6 mg/kg body weight/day, more preferred about 5 mg/kg body weight/day. The daily dose of the compound of formula (I) to be administered will depend on the specific compound employed and on the age and the condition of the patient and it is recommended that the dose of the compound of formula (I) to be given to each individual diabetic patient be determined by a physician.

The compound of formula (I) for use according to the present invention will generally be available in the form of a pharmaceutical composition. Such a composition may be in the form of a powder, a solution, or a suspension, which may or may not be divided in single dose units, or in the form of a capsule or a tablet.

The pharmaceutical composition may comprise carriers, diluents, absorption enhancers and other ingredients which are conventionally used in the art.

The route of administration may be any route which effectively transports the compound of formula (I) to its site of action, the oral or nasal route being preferred.

If a suitably protracted composition is used, the total daily dose can be given in one dose. Alternatively, the total daily dose can be subdivided in two or more smaller doses.

Example 1

Influence of theophyllamine on the blood glucose level in healthy subjects

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Under carefully controlled conditions hypoglycaemia was induced in each of eleven healty subjects by injection of Actrapid® Human insulin, 0.15 IU/kg (available from Novo Nordisk A/S, Bagsvaerd, Denmark). The blood glucose level was monitored from just before the injection of the insulin took place until 2 hours after. The basal level, the nadir level and the level after 1 hour and 2 hours for each subject are given in Table 1 under the entry "placebo".

On a different day a study similar to the one described above was performed on the same subjects, the only difference being that in this second study theophyllamine was administered concomitantly with the insulin. The theophyllamine was administered in the form of a bolus injection of 220 mg per person given at the same time as the insulin followed by a constant rate infusion of theophyllamine of 2,5 mg/kg body weight/hour. The corresponding glucose levels are given in Table 1 under the entry "theophyllamine".

As it appears from Table 1 the nadir level was higher when theophyllamine was given concomitantly with the insulin than when insulin was given alone. Also, the glucose levels were higher 1 and 2 hours after the administration of insulin when theophylline had been given concomitantly than when insulin had been given alone.

TABLE 1

Subject No.	1	2	3	4	5	6	7	8	9	10	11	MEAN	SEM
Basal Level													
Theophyllamine	5.2	5.2	5.9	5.8	5.6	5.7	5.2	5.8	5.0	5.2	5.0	5.4	0.3
Placebo	5.2	5.2	6.2	5.4	5.4	5.3	4.9	5.7	5.5	5.1	4.5	5.3	0.4
Nadir Level													
Theophyllamine	1.5	2.0	1.9	1.6	1.7	2.4	1.5	2.0	1.3	1.3	1.4	1.7	0.5
Placebo	1.5	1.4	1.5	1.4	1.1	1.5	1.2	1.3	1.8	1.0	1.1	1.3	0.3
1 hr after insulin													
Theophyllamine	2.7	3.1	2.8	2.5	3.0	3.8	2.6	3.4	2.0	2.4	2.3	2.8	0.5
Placebo	2.2	2.3	2.9	2.2	2.1	2.7	2.4	2.3	2.3	2.2	1.8	2.3	0.3
2 hr after insulin													
Theophyllamine	3.9	4.3	4.1	3.5	4.5	5.4	4.3	5.1	3.5	2.6	3.1	4.0	0.8
Placebo	2.9	3.1	4.1	2.7	3.0	3.4	3.3	3.2	3.3	2.5	2.9	3.1	0.4

All levels given in mmol/l

Example 2

Influence of theophyllamine on the blood glucose level in diabetic patients

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Under carefully controlled conditions hypoglycaemia was induced in each of nine diabetic patients by injection of Actrapid® Human insulin, 0.15 IU/kg (available from Novo Nordisk A/S, Bagsvaerd, Denmark). The blood glucose level was monitored from just before the injection of the insulin took place until 2 hours after. The basal level, the nadir level and the level after 1 hour and 2 hours for each subject are given in Table 2 under the entry "placebo".

On a different day a study similar to the one described above was performed on the same patients, the only difference being that in this second study theophyllamine was administered concomitantly with the insulin. The theophyllamine was administered in the form of a bolus injection of 220 mg per person followed by a constant rate infusion of theophyllamine of 2,5 mg/kg body weight/hour. The corresponding glucose levels are given in Table 2 under the entry "theophyllamine".

As it appears from Table 2 the nadir level was higher when theophyllamine was given concomitantly with the insulin than when insulin was given alone. Also, the glucose levels were higher 1 and 2 hours after the administration of insulin when theophylline had been given concomitantly than when insulin had been given alone.

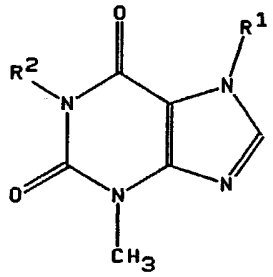
TABLE 2

Subject No.	1	2	3	4	5	6	7	8	9	MEAN
Basal Level										
Theophyllamine	4.8	4.5	5.5	4.6	5.6	4.5	4.7	6.0	4.9	5.0
Placebo	5.5	5.1	4.9	3.8	5.0	5.5	4.5	5.3	4.8	4.9
Nadir level										
Theophyllamine	1.5	1.5	4.1	1.1	1.1	1.7	2.6	1.4	2.2	2.2
Placebo	1.6	1.5	3.0	1.2	1.0	1.4	2.6	1.2	1.9	1.9
1 hr after insulin										
Theophyllamine	2.9	2.1	4.4	1.9	2.1	2.5	2.9	2.1	2.5	2.6
Placebo	2.5	2.1	3.3	1.7	1.6	2.3	2.8	1.9	2.2	2.3
2 hr after insulin										
Theophyllamine	4.8	3.7	6.4	3.1	3.0	3.7	3.8	3.0	3.0	3.8
Placebo	4.4	3.4	4.7	2.4		3.6	3.7	3.1	3.0	3.5

All levels given in mmol/l

CLAIMS

1. The use of a compound of the general formula (I):



(I)

wherein R^1 is hydrogen, methyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 2-nicotinoyloxyethyl, the nicotinic acid salt of 2-hydroxy-3-((2-hydroxyethyl)methylamino)propyl or a lone pair involved in salt formation with the 2-hydroxyethyltrimethylammonium ion and R^2 is hydrogen or methyl; a compound thereof with ethylenediamine or the pharmaceutically acceptable acid addition salts thereof in the manufacture of a pharmaceutical composition useful for counteracting hypoglycaemia in diabetic patients.

2. Use according to claim 1 characterised in that the compound of formula (I) is theophyllamine.

3. Use according to claim 1 characterised in that the compound of formula (I) is theophylline.

4. The use of a pharmaceutical composition according to any one of the preceding claims for counteracting hypoglycaemia in diabetic patients.

5. Any novel feature or combination of features as herein described.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 92/00248

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/52

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO, A1, 8903213 (BILAS, ANDOR) 20 April 1989, see the whole document --	1,4
A	EP, A1, 0300726 (MERCK & CO. INC.) 25 January 1989, see the whole document --	1-4
A	Dialog Information Services, File 351, World Patent Index 81-92, Dialog accession no. 008642126, TSUMURA & CO et al: "New hypoglycaemic agent with high activity - comprises extract from shiratama tea", JP 3083929, A, 910409, 9120 (Basic) --	1-4
A	FR, A, 3577M (M. ALBERT DECORPS) 4 October 1965, see the whole document --	1-4

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
4th December 1992	10 -12- 1992
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Carolina Gomez Lagerlöf

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers 5, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 5 is not clear and concise.

See article 6.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 92/00248

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 30/10/92
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A1- 8903213	89-04-20	AU-D-	2523588	89-05-02
		EP-A-	0339054	89-11-02
EP-A1- 0300726	89-01-25	AU-B-	601862	90-09-20
		AU-D-	1923088	89-01-27
		JP-A-	1104074	89-04-21
		US-A-	5057517	91-10-15
FR-A- 3577M	65-10-04	NONE		